A Case of Chemothermotherapy for Advanced Gastric Cancer

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Abstract: A female patient underwent a total ovario-hysterectomy for metastasis after a gastrectomy, and disseminated peritoneal metastasis was detected. At another hospital, the patient was informed that chemotherapy would not be effective treatment; as a result, she chose to undergo chemothermotherapy at Matsuyama West Hospital. The patient responded to chemothermotherapy, and FDG-PET images showed the disappearance of the disseminated tumor. The quality of life (QOL) for this patient improved remarkably, and she survived for more than 300 days after the treatment.

Key words: advanced gastric cancer, chemothermotherapy, intermittent FP therapy, peritoneal carcimatosis

Introduction

Cancer treatments include surgery, radiotherapy, chemotherapy, and immunotherapy. However, terminal or recurrent cancers do not respond to these treatments and are difficult to treat; therefore, symptomatic therapy must be selected. Recent attention to chemothermotherapy is showing that it is an effective treatment for cancer 1). This is a report of a patient who received chemothermotherapy, as a result of which her QOL improved and her life was prolonged. In addition, the immunological effects of the treatment are reported.
Case

A 57-year-old female patient was being treated in another hospital. She underwent a partial gastrectomy for gastric cancer in October 1997 and a total ovariohysterectomy and postoperative chemotherapy for metastasis from this cancer in March 2001. In June 2002, abdominal pain and general malaise developed, and vomiting and diarrhea began to occur in August 2002. The patient was admitted to the same hospital under a diagnosis of subileus related to disseminated peritoneal metastasis. For this patient, previous chemotherapy with the anticancer agents (5-FU, MTX, PTL) had been ineffective. Therefore, terminal care was recommended. The patient desired thermotherapy and was referred to Matsuyama West Hospital in December 2002.

Table 1. Laboratory findings after admission

<table>
<thead>
<tr>
<th></th>
<th>on admission</th>
<th>302 days after admission</th>
</tr>
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<tbody>
<tr>
<td>Complete blood count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (/μl)</td>
<td>3,400</td>
<td>1,500</td>
</tr>
<tr>
<td>RBC (x10⁶/μl)</td>
<td>285</td>
<td>257</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>8.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>24.2</td>
<td>25.5</td>
</tr>
<tr>
<td>PLT (x10⁴/μl)</td>
<td>23.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP (g/dl)</td>
<td>4.7</td>
<td>7.6</td>
</tr>
<tr>
<td>ALb (g/dl)</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>TB (mg/dl)</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>GOT (IU/ℓ)</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>GPT (IU/ℓ)</td>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>ALp (IU/ℓ)</td>
<td>349</td>
<td>455</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>62</td>
<td>180</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td>Fe (μ/dl)</td>
<td>27</td>
<td>198</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>18.8</td>
<td>9.6</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Tumor marker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA (ng/ml)</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>CA19-9 (u/ml)</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>CA-50 (u/ml)</td>
<td>&lt;1</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>7.3</td>
<td>1,903</td>
</tr>
<tr>
<td>NK cell act. (%)</td>
<td>13.4</td>
<td>42.3</td>
</tr>
</tbody>
</table>

Physical examination on admission: height, 150 cm; body weight, 46 kg; and blood pressure, 110/70 mmHg. Her face exhibited pallor, and malnutrition without jaundice was observed. In the thoracic region, there were no abnormal physical findings, and, in the abdomen, the bulge of a surgical scar and pressure pain were noted. In the bilateral lower limbs, cachexia, including marked edema, was observed. Laboratory data on admission showed normocytic normochromic anemia, hypoproteinemia, hypoalbuminemia, and hypocholesterolemia. The level of alkaline phosphatase was increased;
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however, the levels of tumor markers were within the normal ranges (Table I). Computed tomography (CT) revealed dilatation of the upper abdomen, a solid mesenteric structure in the right lower abdomen, and a funicular structure in the pelvis (Fig. 1). The course of treatment selected included hyperthermia in the upper abdomen (3 times/week, 45 min/set, 1,296 w/set) with a Thermontron RF-8 (Yamamoto Vinyter Co., Ltd., Japan), chemohyperthermia with 10 mg/week of MMC, and total parenteral nutrition (TPN), since oral ingestion was impossible. One month after the start of treatment, abdominal pain, general malaise, abdominal swelling, and cachexia, including marked edema of the lower limbs, gradually subsided. When the total dosage of MMC reached 100 mg, therefore, administration was discontinued due to grade 2 bone marrow suppression, whereas hyperthermia was continued (Fig. 2). At the end of MMC administration, the CT revealed that the solid structure in the lower abdomen had disappeared and that there had been a marked improvement in the ileus. Passage disorder in the pelvic region remained (Fig. 1). Three weeks after the end of MMC administration, intermittent FP therapy (CDDP : 3 mg/day, 5 days/week; 5-FU : 750 mg/day, 3 days/week), which is a procedure of biochemical modulation (BCM), was started. To treat the passage disorder, hyperthermia in the pelvic region was started 20 days after the start of BCM. Because upper abdominal pain recurred 215 days after admission, the hyperthermia site was switched to the upper abdomen. About one month later, the pain subsided. At about 280 days after admission, gastric juice, which had persisted for a long time, had been completely eliminated, facilitating oral ingestion. Therefore, TPN was discontinued, and the QOL also improved. Bone marrow suppression was observed, as described with MMC, and a similar treatment was performed. No serious adverse event occurred, and intermittent FP therapy was eventually discontinued according to the wishes of the patient (Fig. 2).

Fig. 1A. Original CT prior to chemohyperthermia with MMC shows both intestinal distension with mesenteric solid stricture and rectal strand stricture.

Fig. 1B. CT after chemohyperthermia with MMC shows the disappearance of both intestinal distension and mesenteric solid stricture; however, the rectal passage failure is still present.
Fig. 2. Clinical course

Fig. 3A. CT prior to chemohyperthermia with intermittent FP therapy shows distension of both the intestine and rectum.

Fig. 3B. CT two months after chemohyperthermia with intermittent FP therapy shows the disappearance of both intestinal (distension) and rectal distension.
The passage disorder, which had been discovered through CT at the onset of recurrent upper abdominal pain, had improved markedly within two months of detection (Fig. 3).

However, the area where the passage disorder had been detected was not enhanced in the CT. In that area, fluorodeoxyglucose-positron emission tomography (FDG-PET) showed that the accumulation had been enhanced at two points, and this finding disappeared within two months of the chemohyperthermia (Fig. 4).

The levels of ferritin and NK cell activity gradually increased after admission. The ferritin level at 300 days after admission was 260 times higher than it had been on admission.

The NK cell activity also increased from 13.4% to 47.3% (Fig. 5).

Hypoalbuminemia and hypocholesterolemia, which were observed on admission, improved to normal levels approximately 300 days after admission; however, there were no changes in the alkaline phosphatase level (Table I).

**Discussion**

Currently, symptomatic therapy is performed to treat terminal gastric cancer with disseminated peritoneal metastasis; however, the prognosis is poor. Recently, Nakabayashi et al. reported a new treatment; they inserted a 24-F silicon tube into the peritoneal cavity during a gastrectomy for progressive gastric cancer with peritoneal dissemination. The chemothermotherapy group, in which intraperitoneal administration of CDDP was combined with thermotherapy 2 weeks after surgery, showed a better prognosis than the surgery group. However, when intestinal adhesion related to gastrectomy and additional surgery or ileus related to disseminated peritoneal metastasis are observed, as in this case,
intraperitoneal administration of anticancer agents is difficult. Therefore, we carried out thermotherapy combined with systemic administration of antitumor agents.

In this patient, an issue was ineffectiveness of multiple drug, however, chemothermotherapy with MMC was performed because results of basic studies have shown that heat enhances the effects of anticancer agents and that, in MMC-resistant Chinese hamster-derived ovary cells, cell killing is enhanced at 43°C or higher.

In clinical practice, MMC is commonly used for chemothermotherapy in patients with digestive cancer. Thus, improvement of the symptoms in the upper abdominal area and cachexia, such as edema of the lower limbs, was achieved.

Despite the improvement of symptoms in the upper abdominal area, there was a passage disorder in the pelvic region.

As the total dosage of MMC reached 100 mg, continuous administration of this agent proved to be difficult; therefore, intermittent FP therapy was performed with a BCM procedure. Scanlon et al. and Shirasaka et al. have established a basic theory that, in BCM, low-dose CDDP acts on the cellular membrane as a modulator and inhibits the intracellular uptake of methionine, enhancing the effects of 5-FU as an effector. Intermittent FP therapy was developed by improving continuous FP therapy, with the purpose of saving normal cells. With respect to the results of using this procedure for the treatment of digestive cancer, a high response rate, the relief of side effects, and the prolongation of the administration period have been reported. In the present patient, resistance to 5-FU was indicated. However, since Shiu et al. and Murakami et al. have reported that hyperthermia over 43°C enhances the effects of 5-FU, chemothermotherapy was performed by intermittent FP therapy, and the effects were consistent with those reported by Yamamitsu et al. The QOL was improved without adverse reactions except for mild bone marrow suppression.

A procedure was developed to relieve bone marrow suppression; however, it caused more severe side effects.
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effects (grade 3) than MMC. This may have been associated with the massive administration of MMC prior to intermittent FP therapy. Generally, CT is used to evaluate the effects of chemothermotherapy; however, FDG-PET is used in tumor diagnosis. In particular, Kurosaki et al.13) have reported that glucose metabolism with 18F-fluorodeoxyglucose (FDG) provides information that cannot be obtained by standard morphological diagnosis, facilitating a more accurate evaluation. In the present patient, an ordinary CT showed enhanced accumulation at two points.

In addition, the symptoms subsided 2 months after the start of treatment, and FDG-PET showed that the accumulation had disappeared, suggesting that this procedure is more accurate than CT for evaluating the treatment response. Thermotherapy increases NK cell activity,14) which is considered its indirect effect. In the present patient, NK cell activity also increased, although bone marrow suppression was observed during intermittent FP therapy. It was speculated that the thermal effects of this procedure may have overcome the influence of bone marrow suppression and that the improvement in parasympathetic actions may have been related to the improvements in the clinical symptoms.

It also resulted in an increase of the relaxation period, which persistently increased the NK cell activity and exhibited antitumor effects.

It appears then that the intermittent FP therapy led to the decay of the cancer cells via the direct effects of thermotherapy, in other words, it had tumoricidal effects, and that ferritin was released into the blood, resulting in a gradual increase.

In MMC therapy, there were no increases in NK cell activity or in the ferritin level. Concerning NK cell activity, MMC-related bone marrow suppression may have been involved; however, concerning the ferritin level, an etiological factor is unclear, although the influence of MMC cannot be ruled out.

Chemothermotherapy by systemic administration of anticancer agents to patients with terminal gastric cancer, in whom it was expected that multiple drug resistance would make the prognosis poor, exhibited antitumor effects, improved the QOL, and has prolonged a patient’s survival by, so far, 300 days. In particular, chemothermotherapy by intermittent FP therapy increased the immune capacity, which suggests its usefulness.

References


温熱化学療法が有効であった末期胃癌の1例

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2 松山西病院内科
3 松山西病院放射線技師
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要  旨：播種性腹膜転移を来たした末期胃癌は予後不良であり、積極的治療は行なわれていないのが現状である。今回、我々は胃切除術後子宮全摘除術および化学療法を施行された後に播種性腹膜転移を来し、制癌剤に耐性を呈した末期胃癌患者に対して温熱化学療法を行なった。この結果、抗腫瘍効果とQOLの改善を認め、300日以上の延命効果を得ることができ、現在も治療中である。本法の有効性が免疫学的、画像診断の経過を含めて、立証されたと考えられた。